Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

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- 1. (Previously Presented) A substantially pure preparation of a plasmin inhibitor characterised in that it is a single stage competitive inhibitor of plasmin, wherein "substantially pure" means that at least 60% of the total material in the preparation is the plasmin inhibitor.
- 2. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $1 \times 10^{-8} \text{ M}^{-1}$ to $1 \times 10^{-10} \text{ M}^{-1}$.
- 3. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $5x10^{-8}$ M⁻¹ to $8x10^{-9}$ M⁻¹.
- 4. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $1x10^{-9}$ M⁻¹ to $5x10^{-9}$ M⁻¹.
- 5. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $4x10^{-5}$ sec⁻¹ M⁻¹ to $5x10^{-7}$ sec⁻¹ M⁻¹.
- 6. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $1 \times 10^{-6} \text{ sec}^{-1} \text{ M}^{-1}$ to $1 \times 10^{-7} \text{ sec}^{-1} \text{ M}^{-1}$.
- 7. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $2x10^{-6}$ sec⁻¹ M⁻¹ to $9x10^{-6}$ sec⁻¹ M⁻¹.
- 8. (Currently Amended) The plasmin inhibitor of claim 1 comprising a polypeptide selected from the group consisting of:

- (a) Lys-Asp-Arg-Pro-Asp-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Lys-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:2];
- (b) Lys-Asp-Arg-Pro-Glu-Leu-Cys-Glu-Leu-Pro-Pro-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Gln-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:4];
- (c) Lys-Asp-Arg-Pro-Asn-Phe-Cys-Lys-Leu-Pro-Ala-Glu-Thr-Gly-Arg-Cys-Asn-Ala-Lys-Ile-Pro-Arg-Phe-Tyr-Tyr-Asn-Pro-Arg-Gln-His-Gln-Cys-Ile-Glu-Phe-Leu-Tyr-Gly-Gly-Cys-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Lys-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:6];
- (d) Lys-Asp-His-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Glu-Thr-Gly-Ser-Cys-Lys-Gly-Asn-Val-Pro-Arg-Phe-Tyr-Tyr-Asn-Ala-Asp-His-His-Gln-Cys-Leu-Lys-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Glu-Glu-Gly-Lys-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:8];
- (e) Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Leu-Pro-Asp-Thr-Gly-Ser-Cys-Glu-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Thr-Arg-Asp-Arg-Glu-Cys-Glu-Cys-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:10]; and
- Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Ile-Gly-Pro-Trp-Asp-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Pro-Arg-Glu-His-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Lys-Gly-Asn-Ala-Asn-Asn-Phe-Asn-Thr-Gln-Glu-Gln-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:12].
- 9. (Currently Amended) The plasmin inhibitor of claim 1, comprising a polypeptide having the general formula:

KDZPZŸCZLBBZBGXCZXXXBXFÃYXBZZZZCBZFBYGGCXBNANNFXTXEECESTC AA (I) (SEQ ID NO 67), wherein:

X is any amino acid selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val, aaminobutyric acid, L-N-methylalanine, α-amino-α-methylbutyrate, L-Nmethylarginine, aminocyclopropane-carboxylate, L-N-methylasparagine, aminoisobutyric acid, L-N-methylaspartic acid, aminonorbornyl-carboxylate, L-N-methylcysteine, cyclohexylalanine, L-N-methylglutamine, cyclopentylalanine, L-N-methylglutamic acid, L-N-methylisoleucine, L-Nmethylhistidine, D-alanine, L-N-methylleucine, D-arginine, L-N-methyllysine, D-aspartic acid, L-N-methylmethionine, D-cysteine, L-N-methylmorleucine, Dglutamate, L-N-methylnorvaline, D-glutamic acid, L-N-methylornithine, Dhistidine, L-N-methylphenylalanine, D-isoleucine, L-N-methylproline, Dleucine, L-N-medlylserine, D-lysine, L-N-methylthreonine, D-methionine, L-Nmethyltryptophan, D-ornithine, L-N-methyltyrosine, D-phenylalanine, L-Nmethylvaline, D-proline, L-N-methylethylglycine, D-serine, L-N-methyl-tbutylglycine, D-threonine, L-norleucine, D-tryptophan, L-norvaline, D-tyrosine, α-methyl-aminoisobutyrate, D-valine, α-methyl-γ-aminobutyrate, D-αmethylalanine, α -methylcyclohexylalanine, D- α -methylarginine, α methylcylcopentylalanine, D-α-methylasparagine, α-methyl-α-napthylalanine, D-α-methylaspartate, α-methylpenicillamine, D-α-methylcysteine, N-(4aminobutyl)glycine, D-α-methylglutamine, N-(2-aminoethyl)glycine, D-αmethylhistidine, N-(3-aminopropyl)glycine, D-α-methylisoleucine, N-amino-αmethylbutyrate, D- α -methylleucine, α -napthylalanine, D- α -methyllysine, Nbenzylglycine, D-α-methylmethionine, N-(2-carbamylediyl)glycine, D-αmethylornithiine, N-(carbamylmethyl)glycine, D-α-methylphenylalanine, N-(2carboxyethyl)glycine, D-α-methylproline, N-(carboxymethyl)glycine, D-αmethylserine, N-cyclobutylglycine, D-α-methylthreonine, N-cycloheptylglycine, D-α-methyltryptophan, N-cyclohexylglycine, D-α-methyltyrosine, Ncyclodecylglycine, L- α -methylleucine, L- α -methyllysine, L- α -methylmethionine,

L-α-methylnorleucine, L-α-methylnorvatine, L-α-methylornithine, L-α-methylphenylalanine, L-α-methylproline, L-α-methylserine, L-α-methyltryptophan, L-α-methyltyrosine, L-α-methyltyrosine, L-α-methyltyrosine, L-α-methylvaline, L-N-methylhomophenylalanine, N-(N-(2,2-diphenylethyl carbamylmethyl)glycine, N-(N-(3,3-diphenylpropyl carbamylmethyl)glycine, and 1-carboxy-1-(2,2-diphenyl-ethyl amino)cyclopropane;

- Ÿ is a hydrophobic amino acid;
- à is an aromatic amino acid;
- Z is K, R, H, D, E, Q or N; and
- B is a neutral amino acid, or P, A, G, S, T, V or L.
- 10. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 3 is H or R.
- 11. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 5 is K, N, E or D.
- 12. (Original) The plasmin inhibitor of claim 9, wherein the Y at position 6 is F or L.
- 13. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 8 is E or K.
- 14. (Original) The plasmin inhibitor of claim 9, wherein the B at position 10 is P or L.
- 15. (Original) The plasmin inhibitor of claim 9, wherein the B at position 11 is P or A.
- 16. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 12 is E or D.
- 17. (Original) The plasmin inhibitor of claim 9, wherein the B at position 13 is T or I.
- 18. (Original) The plasmin inhibitor of claim 9, wherein the X at position 15 is P, S or R.
- 19. (Currently Amended) The plasmin inhibitor of claim 9, wherein the Z at position 17 is K, N, E, D or R.
- 20. (Original) The plasmin inhibitor of claim 9, wherein the X at position 18 is D, G, A or V.

- 21. (Original) The plasmin inhibitor of claim 9, wherein the X at position 19 is F, N, K or R.
- 22. (Original) The plasmin inhibitor of claim 9, wherein the X at position 20 is T, P, F or I.
- 23. (Original) The plasmin inhibitor of claim 9, wherein the B at position 21 is G, V or P.
- 24. (Original) The plasmin inhibitor of claim 9, wherein the X at position 22 is A, S or R.
- 25. (Original) The plasmin inhibitor of claim 9, wherein the A at position 24 is Y or H.
- 26. (Original) The plasmin inhibitor of claim 9, wherein the X at position 26 is S or N.
- 27. (Original) The plasmin inhibitor of claim 9, wherein the B at position 27 is P, A or T.
- 28. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 28 may be D or R.
- 29. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 29 is E, D, H or Q.
- 30. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 30 is H, K, R or Q.
- 31. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 31 is K, Q or E.
- 32. (Original) The plasmin inhibitor of claim 9, wherein the B at position 33 is L or I.
- 33. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 34 is E or K.
- 34. (Original) The plasmin inhibitor of claim 9, wherein the B at position 36 is L or I.
- 35. (Original) The plasmin inhibitor of claim 9, wherein the X at position 41 is E, G or K.
- 36. (Original) The plasmin inhibitor of claim 9, wherein the B at position 42 is C or G.
- 37. (Original) The plasmin inhibitor of claim 9, wherein the X at position 48 is K, N or I.
- 38. (Original) The plasmin inhibitor of claim 9, wherein the X at position 50 is K, Q or I.
- 39. (Previously Presented) The plasmin inhibitor of claim 8 or claim 9, wherein the polypeptide comprises a leader peptide comprising the sequence:- Met-Ser-Ser-Gly-Gly-Leu-

Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser [SEQ ID NO:14].

- 40. (Original) The plasmin inhibitor of claim 39, wherein the polypeptide is selected from the group consisting of:-
 - (a) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Asp-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Lys-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:16];
 - (b) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Glu-Leu-Cys-Glu-Leu-Pro-Pro-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Gln-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:18];
 - (c) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Asn-Phe-Cys-Lys-Leu-Pro-Ala-Glu-Thr-Gly-Arg-Cys-Asn-Ala-Lys-Ile-Pro-Arg-Phe-Tyr-Tyr-Asn-Pro-Arg-Gln-His-Gln-Cys-Ile-Glu-Phe-Leu-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Lys-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:20];
 - (d) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-His-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Glu-Thr-Gly-Ser-Cys-Lys-Gly-Asn-Val-Pro-Arg-Phe-Tyr-Tyr-Asn-Ala-Asp-His-His-Gln-Cys-Leu-Lys-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Phe-Lys-Thr-Ile-Glu-Gly-Lys-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:22];
 - (e) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Leu-Pro-Asp-Thr-Gly-Ser-Cys-Glu-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Thr-Arg-Asp-Arg-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala; [SEQ ID NO:24]; and
 - (f) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Ile-Gly-Pro-Trp-Asp-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Pro-Arg-Glu-His-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Lys-Gly-Asn-Ala-Asn-Asn-Phe-Asn-Thr-Gln-Glu-Gln-Cys-Glu-Ser-Thr-Cys-Ala-Ala; [SEQ ID NO:26].
- 41. (Withdrawn) An isolated polynucleotide encoding the polypeptide of claim 8.

- 42. (Withdrawn) An isolated polynucleotide selected from the group consisting of:
 - (a) AAGGACCGTCCGGATTTCTGTGAACTGCCTGCTGACACCGGACCATGTA GAGTCAGATTCCCATCCTTCTACTACAACCCAGATGAAAAAAAGTGCTAGAG TTTATTTATGGTGGATGCGAAGGGAATGCTAACAATTTTATCACCAAAGAGG AATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:1];
 - (b) AAGGACCGTCCAGAGTTGTGTGAACTGCCTCCTGACACCGGACCATGTA GAGTCAGATTCCCATCCTTCTACTACAACCCAGATGAACAAAAATGCCTAGA GTTTATTTATGGTGGATGCGAAGGGAATGCTAACAATTTTATCACCAAAGAG GAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:3];
 - (c) AAGGACCGTCCAAATTTCTGTAAACTGCCTGCTGAAACCGGACGATGTA ATGCCAAAATCCCACGCTTCTACTACAACCCACGTCAACATCAATGCATAGA GTTTCTCTATGGTGGATGCGGAGGGAATGCTAACAATTTTAAGACCATTAAG GAATGCGAAAGCACCTGTGCTGCATGA [SEQ ID NO:5];

 - (e) AAGGACCGTCCAAAATTCTGTGAACTGCTTCCTGACACCGGATCATGTGA AGACTTTACCGGAGCCTTCCACTACAGCACACGTGATCGTGAATGCATAGAG TTTATTTATGGTGGATGCGGAGGGAATGCTAACAATTTTATCACCAAAGAGG AATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:9];
 - (f) AAGGACCGTCCAAAGTTCTGTGAACTGCCTGCTGACATCGGACCATGGG ATGACTTTACCGGAGCCTTCCACTACAGCCCACGTGAACATGAATGCATAGA GTTTATTTATGGTGGATGCAAAGGGAATGCTAACAACTTTAATACCCAAGAG CAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:11];
 - (g) a biologically-active polynucleotide fragment of any one of SEQ ID NOS 1, 3, 5, 7, 9, 11, 12, 14, 16, 18 and 20; and
 - (h) a polynucleotide homologue of any of the foregoing sequences.
- 43. (Withdrawn) The polynucleotide of claim 42 further comprising a nucleotide sequence encoding a leader peptide.
- 44. (Withdrawn) The polynucleotide of claim 43, wherein the nucleotide sequence comprises the sequence:-

ATGTCTTCTGGAGGTCTTCTCCTGCTGGGACTCCTCACCCTCTGGGAGGTG CTGACCCCGTCTCCAGC [SEQ ID NO:13] or a biologically active fragment thereof, or a polynucleotide homologue of these.

- 45. (Withdrawn) The polynucleotide of claim 43, wherein said polynucleotide is selected from the group consisting of:

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TGAACATGAATGCATAGAGTTTATTTATGGTGGATGCAAAGGGAATGCTAAC AACTTTAATACCCAAGAGCAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:25]; and

- 46. (Original) A pharmaceutical composition for alleviating blood loss in a patient, said composition comprising the polypeptide of claim 8 and a pharmaceutically acceptable carrier.
- 47. (Withdrawn) A method for alleviating blood loss comprising the step of administering to a patient in need of such treatment a therapeutically effective dosage of the polypeptide of claim 8 in combination with a pharmaceutically acceptable carrier.
- 48. (Withdrawn) An anti-tumour agent comprising the polypeptide of claim 8 conjugated with an anti-fibrin antibody.
- 49. (Currently amended) The plasmin inhibitor of claim 1, comprising the amino acid sequence ECESTCAA (SEQ ID NO. 68).
- 50. (Currently amended) The plasmin inhibitor of claim 1, further comprising the amino acid sequence NANNF (SEQ ID NO. 69).
- 51. (Currently amended) The plasmin inhibitor of claim 49, further comprising the amino acid sequence YGGC (SEQ ID NO. 70).
- 52. (Previously Presented) The plasmin inhibitor of claim 1, which is conjugated to an antifibrin antibody.
- 53. (Previously Presented) The plasmin inhibitor of claim 1, wherein "substantially pure" means that at least 75% of the total material in the preparation is the plasmin inhibitor.

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- 54. (Previously Presented) The plasmin inhibitor of claim 1, wherein "substantially pure" means that at least 90% of the total material in the preparation is the plasmin inhibitor.
- 55. (Previously Presented) The plasmin inhibitor of claim 1, wherein "substantially pure" means that at least 95% of the total material in the preparation is the plasmin inhibitor.

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